H1N1: A Mexican Perspective

In April this year, a new influenza virus of swine origin emerged in Mexico and spread rapidly around the world. As the Northern hemisphere winter flu season kicks off, Laura Vargas-Parada reports on the measures that Mexico is taking to combat the H1N1 pandemic.

Although Mexico has been actively engaged in establishing a health emergency response network for a decade, the emergence of the pandemic (H1N1) 2009 flu virus this Spring put the network under intense pressure and prompted evaluation of omissions and unexpected outcomes. One major flaw in the Preparedness and Response Plan was that "all possible scenarios considered that the potential risk would arrive from abroad, most likely from Asia, giving us time to react to the emergency. We never expected the epidemic to start here," explains Mexico's health minister José Angel Córdova. "In a matter of hours important decisions had to be taken with the scarce information we had at hand," he adds. Ignacio Villaseñor, undersecretary of health for Mexico City's local government, emphasizes that "at that moment, what we needed to achieve was that those that were healthy not to get sick, those that were sick not to develop severe disease, and those who developed severe disease not to die." Strict measures to prevent the spread of the H1N1 virus were implemented. "This was a new virus; no one knew how virulent it was or its capacity for transmission so we were extremely cautious. Putting it into perspective, now we know the disease is not as severe as it was expected…but not at that time," says Córdova. Mexico was the only country during the emergence of the H1N1 pandemic to establish a broad-based strategy for school closures and bans on public gatherings; in Mexico City, the world's third largest metropolis, all nonessential activities were shut down. It is estimated that the pandemic cost Mexico ~$4 billion dollars (0.4% of its GDP).

One of the major questions raised during the Spring pandemic was the death toll observed in Mexico and not elsewhere. "A retrospective analysis of the epidemiological data has shown that one main contributing factor for the death of patients was the delayed admission and delayed initiation of antiviral treatment," explains Córdova. In Mexico, most people who get the flu never go to a doctor. Even worse, it is common for people to self-diagnose and to treat themselves with homemade remedies or, as few drugs require a prescription, they simply buy them at the drugstore. "With a massive media campaign, people are now looking for medical attention at the onset of symptoms and the death rate has diminished to be currently similar to what is reported globally. Before April 23 people took up to nine days to see a doctor, now the average is a day and a half," says Córdova.

As of December 2 this year, there have been 66,070 confirmed cases of pandemic H1N1 (2009) flu and 671 deaths in Mexico (for comparison, according to the National System on Health Information, there were 14,575 deaths from acute respiratory infections in 2007). Much has been learned from the early days of the H1N1 (2009) pandemic and many changes have been implemented in time for this winter's flu season.

Lessons Learned

Vaccines

So far this year, the Mexican government has invested ~$330 million to buy general supplies, antivirals, vaccines, laboratory equipment, mechanical ventilators, and monitors for acute care. The purchase of H1N1 2009 vaccine alone is expected to cost ~$200 million. In the US, 250 million doses of swine flu vaccine have been ordered at a cost of $1.5 billion and the US Congress has set aside $7.65 billion to fight pandemic flu. According to the US Centers for Disease Control and Prevention (CDC), as of December 4 there were 73 million doses of H1N1 vaccine available in the US. Like many other countries, Mexico has been struggling to obtain a sufficient supply of H1N1 flu vaccine. A recent agreement with the French pharma company Sanofi-Aventis enabled Mexico to obtain 865,000 doses of Panenza vaccine last month (215,000 doses from France and 650,000 doses from the US). The next batch "will arrive between December and March to complete a total of 30 million," says Alejandro Macías, special commissioner of the Federal Government for human influenza and assistant director at the National Institute of Medical Sciences and Nutrition. Sanofi-Aventis is supplying 20 million doses, and GlaxoSmith-Kline (GSK) is providing an additional 10 million doses of its H1N1 pandemic vaccine with adjuvant (Arepanrix) manufactured in Canada. "As the number of vaccines is limited, there will be a program to prioritize health-care workers, pregnant women, children from six months to three years old, as well as individuals at risk of severe disease, such as people with chronic underlying illnesses," says Macías. As for seasonal influenza vaccination, since October 5, 20 million doses have been given to health-care workers, children, the elderly, and those over 50 with conditions like asthma, diabetes, or obesity. "We expect to complete seasonal vaccination by December," adds Macías. Seasonal influenza vaccination was introduced in Mexico as part of the annual national vaccination campaign in 2004. To assure the efficient allocation of both vaccines and antivirals, "we have implemented a central logistics and delivery system," explains Córdova. Both vaccines and antivirals are being distributed by Biologicals and Reactives of Mexico (BIRMEX), "which has a very well established network," says Macías. (BIRMEX is a state-owned company that produces, distributes, and imports vaccines, heterologous sera, and clinical diagnostic products).

Many have complained that the shortage of H1N1 flu vaccine is a result of the monopoly imposed by the countries where the vaccine is produced. "For decades, Mexico produced all the vaccines that were applied in the country. However, very bad political decisions reduced our capability to mainly commercialize and distribute the vaccines and products others produce," explains infectious diseases expert Samuel Ponce de León, a former medical director for Bristol-Myers Squibb in Mexico and current director of BIRMEX. "At the end of 2007, BIRMEX acquired a production plant with the aim of regaining capability to produce vaccines and established an agreement with Sanofi-Aventis for the technological transfer and construction of a plant for producing seasonal influenza vaccine." With an investment of $250 million, the plant, located in the State of Mexico, will initiate security and stability tests in 2011 and is expected to start producing around 25 million doses of vaccine by 2012. Ponce de León adds, "it has been a great mistake not to have given priority to investment in the development of science and technology" as it is clearly becoming a matter of national security.

Public Health

The winter flu season in Mexico is expected to peak next month, and an agreement has been reached that public health hospitals will reserve at least 12% of their beds for pandemic flu patients. "To expand hospital capacity, parking lots and classrooms will be equipped to receive the patients, non-essential activities like elective surgeries will be suspended, and those patients that can be taken care of at home will be discharged," says Córdova. In Mexico City, the local government has designated two separate hospitals for the management of adults and children with pandemic flu. The remaining 26 local hospitals and 220 outpatient clinics will remain open during evenings and weekends to assist people seeking medical attention.

As people are being advised to consult a physician at the first signs of flu symptoms like fever and cough, triage will be important for distributing scarce resources in a rational manner. "We have found that … *caravanas de la salud* are very useful," says Córdova. Launched in 2007, *caravanas de la salud* is a nationwide system of mobile healthcare (medical and dental) clinics operated by physicians and nurses that provide regular primary care to low-income individuals living in remote areas throughout the country. "During the early outbreak they gave thousands of medical consults, resolving many of the enquiries and reducing the number of people visiting the hospitals," says Córdova.

A key measure to counter the flu season this winter is a health promotion and prevention program. "We need to create a culture of prevention," says Esther Orozco, general director of the Institute of Science and Technology of Mexico City. Córdova notes that "a major strategy in our program for the winter season is the training of personnel. Different workshops have been put in place at three major levels: physicians and nurses (to standardize diagnosis and treatment), hospital staff members (to respond to the need for adequate hospital infrastructure), and state health ministers." Guides, educational material, and handbooks used in the workshops as well as information for the general public are available online (http://www.promocion.salud.gob.mx/dgps/interior1/influenza_estacional.html).

Despite all of these efforts, Mexico still lags behind other countries in investing in public health. In 2007, for example, Mexico invested 5.9% of its GDP on health, compared with an average of 9.1% for members of OECD (Organisation for Economic Cooperation and Development) and 16% for the US (http://stats.oecd.org/Index.aspx?datasetcode=SNA_TABLE1). The public health expenditure per capita for the same year was $372 in Mexico compared with $3310 in the US.

Diagnostics

A major problem with the H1N1 pandemic flu outbreak in April was meeting the demand for rapid diagnosis. At that time, only the Institute of Epidemiological Diagnosis and Reference (InDRE) in Mexico City (Mexico's National Public Health Laboratory) had the facilities to implement the CDC's protocol for using RT-PCR to detect the influenza A (H1N1) 2009 virus strain. Major investments were made after the outbreak to upgrade Mexico's diagnostic laboratory network. Currently, 27 state public health laboratories (out of 31), 1 laboratory in the Mexican Institute for Social Security network, and 3 (out of 12) of the National Institutes of Health in Mexico City are now equipped to use RT-PCR to detect the H1N1 virus. This month, Mexico City expects to open its own fully equipped state public health laboratory at the University of Mexico City.

For seasonal influenza, "28 state laboratories have the capability to determine if the samples sent by sentinel surveillance clinics are influenza A or B by means of immunofluorescence assays," says InDRE deputy director Celia Alpuche-Aranda. "All positive samples for influenza, and 10% of the negative ones are then sent for confirmation to InDRE. If positivity is confirmed then subtyping (H1, H3, and H5) is done and a viral isolate obtained. For subtyping, we use the hemagglutination-inhibition test and RT-PCR. Samples are sent to CDC, our collaborative center in the Flu-Net network," she says. "Surveillance for [pandemic (H1N1) virus] mutations is done by sequencing the neuraminidase gene. Up to now, 106 different clinical specimens collected from different dates and locations have been analyzed and all have been shown to be susceptible to neuraminidase inhibitors," adds Alpuche-Aranda. "Selected virus isolates mainly from severe hospitalized cases and deaths will be fully sequenced using CDC's overlapping forward and reverse primers. At this moment we are standardizing the technique," she says.

Science and Policy

With most of the laboratory work focusing on diagnosis, there has been little time for monitoring emerging mutations and viral reassortants. One way to solve this limitation "would be to bring in academic labs outside of the government testing system, but sharing of clinical materials and trust is low," says Susana López Charretón, a virologist from the Institute of Biotechnology at the National University of Mexico (UNAM). "We can provide state-of-the art technology and human resources to help them [but] there was no response, no sign of interest. We could have collaborated in the analysis of a national seroepidemiology survey to know how many people have been already exposed to the virus," she says.

Another problem that surfaced with the outbreak was the lack of trained personnel to respond to an emergency of this type. "We are still a very small scientific community and are in desperate need of more virologists" says López Charretón.

The perception of a lack of collaboration between clinical and other researchers, and between government laboratories and academia across the country, is a major concern. "During this epidemic, policy makers failed to recognize what public universities had to offer: the power of a well-established scientific community that was ready to help in harnessing the best available knowledge to solve the country's problems," says Antonio Lazcano, an evolutionary biologist at UNAM. "We were severely criticized for sending samples of the suspected cases to the Public Health Agency of Canada and the US Centers for Disease Control and Prevention," says Alpuche-Aranda. "In Mexico, we have first level research groups, but none of them had experience, neither the primers nor the probes, to isolate unknown pathogens. We were in a rush to sort out what was going on. Besides, the World Health Organization requires a set of standards to safely handle and work with new pathogens," she explains. Fátima Fernández Christlieb, a sociologist at UNAM, points out that "the new influenza virus highlighted a large list of shortages, among them, the lack of coordination within the academic community and the absence of links between academia and those who make the decisions that affect the country." Córdova concedes: "We worked together. Still, we need to work out a better strategy for collaborating with academia."

Another issue of concern is that although Mexican researchers compiled valuable information during the initial H1N1 influenza outbreak, very few articles have been published in peer-reviewed journals. Villaseñor explains, "[at that time] we were overloaded with surveillance and field work and did not have enough staff." A team led by Lazcano chose to publish a preliminary evolutionary analysis of the virus on their own blog page "with the goal of reaching a much broader audience," Lazcano explains. For Gustavo Cruz Pacheco, at UNAM's Institute of Applied Mathematics, who studied the dynamics of the outbreak when control measures were implemented, the difficulty was to cross disciplines and publish in biology journals.

As the winter flu season proceeds, Mexico continues to look for ways to bolster public health programs and to make better use of its scientists and research facilities. As Córdova points out, "there will always be problems. And the best way to face them is not by hiding them, but to bring them forward, ask for all the support needed, and make all decisions based upon the best available scientific data." Carlos Arias, director of the Biotechnology Institute at UNAM, concurs: "The only way to make decisions and establish public policies is through the knowledge and evidence that comes from scientific research." From the point of view of policy implementation, Orozco says, "most Mexican politicians are scientifically illiterate and do not have a vision about the importance of science. That is why, although we can say we have science, that won't be enough while decision-makers do not recognize the power of scientific research in making policies on the basis of evidence. As a country we need to know why we want science, which are the plans, the projects, the route, the aims that we want to achieve by means of science and technology."

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